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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/724,319	SCHENK, DALE B.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-58,61,63-66,71-79,81,85,86,92-94,97,99,164-191,194-205 and 207-209* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 56-58,61,63-66,71-79,81,85,86,92-94,97,99,164-191,194-205 and 207-209.

DETAILED ACTION

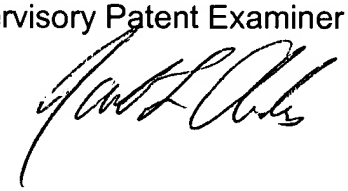
Formal Matters

1. In view of the appeal brief filed on October 1, 2006, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below: 

2. Applicant has previously canceled claims 1-55, 59, 60, 62, 67-70, 80, 82, 84, 87-91, 95, 96, 98, 100, 192, 193 and 206. Claims 83 and 101-163 have been canceled by Applicant as requested in the after final amendment filed October 10, 2006. Following the amendment, claims **56-58, 61, 63-66, 71-79, 81, 85, 86, 92-94, 97, 99, 164-191, 194-205** and **207-209** are pending and under examination in the current office action.

3. The Examiner of U.S. Patent Application No. 09/724,319 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Ballard, Technology Center 1600, Art Unit 1649.

Priority

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed provisional application, Application Nos. 60/067,740, filed 12/02/1997, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. There is no disclosure or support for the 266 monoclonal antibody in the '740 application, nor for any anti-Aβ antibodies specifically binding to an epitope within Aβ 13-28. Support for these claimed limitations is first documented in provisional

application No. 60/080,970, filed April 7, 1998. Accordingly, for purposes of prior art, the effective filing date of the instant claims is **April 7, 1998**.

Withdrawn Claim Rejections

5. The rejection of claims 56-58, 61, 63-66, 71-79, 81, 85-86, 92-94, 97, 99, 1664-191, 194-205 and 207-209 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 43-44, 134-135, 138-139, 142-145, 146, 148 and 154-157 of Application No. 09/979,701 is moot in view of the fact that the '701 application has been abandoned.

6. The rejection of claims 56-58, 61, 63-66, 71-79, 81, 85-86, 92-94, 97, 99, 164-191, 194-205 and 207-209 under 35 U.S.C. 112, first paragraph (written description / new matter), as set forth at ¶ 11 of the previous office action mailed May 2, 2006, is withdrawn upon further consideration by the Examiner.

7. The rejection of claims 56-58, 61, 63-66, 71-79, 81, 85-86, 92-94, 183-191, 194-205 and 207-209 under 35 U.S.C. 112, first paragraph (scope of enablement), as set forth at ¶ 12 of the previous office action mailed May 2, 2006, is withdrawn in view of Applicant's argument and upon further consideration by the Examiner.

8. Applicant's arguments, see section 7.4.3 of the appeal brief filed January 9, 2007, with respect to claims 56-58, 61, 63-66, 71-79, 81, 85-86, 92-94, 97, 99, 164-191,

194-204 and 207-209 have been fully considered and are persuasive. The rejection of claims 56-58, 61, 63-66, 71-79, 81, 85-86, 92-94, 97, 99, 164-191, 194-204 and 207-209 under 35 U.S.C. 103(a) has been withdrawn.

New Claim Objections and Claim Rejections

Claim Objections

9. Claim 57 is objected to because of the following informalities: the claim does not recite the name of the particular monoclonal antibody, 266, and contains a sentence fragment recited in another claim, "for binding to Aβ" – both of which appear to be typographical errors. It is assumed that the claim is meant to recite "wherein the humanized antibody is a humanized version of the monoclonal antibody 266 (ATCC accession number PTA-6123)." Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 57 and 184 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Claim 57 is drawn to a method of treating a patient having Alzheimer's disease, comprising administering to the patient a composition comprising a humanized version of the monoclonal 266 antibody. Claim 184 is dawn to a method of reducing risk or delaying onset of Alzheimer's disease in a patient at risk of the disease, comprising administering a composition comprising a humanized version of the monoclonal 266 antibody.

The nature of the invention is the demonstration that administration of particular anti-Aβ antibodies reduces amyloid-β plaque burden in the brains of transgenic PDAPP mice, which are an animal model of Alzheimer's disease. The instant specification, beginning at p. 72, discloses results of experiments in which different antibodies raised against Aβ were administered to the PDAPP mice. Whereas mice treated with a polyclonal anti-Aβ42 antibody had significantly reduced cortical, hippocampal and cerebellar Aβ levels, cortical and hippocampal levels of Aβ were not significantly reduced in mice treated with the monoclonal antibody (mAb) 266. The 266 mAb did show a slight reduction of Ab levels in the cerebellum, however, since this is a region "typically minimally affected with AD pathology" (see p. 53, lines 27-28), it is unclear that

a reduction in Aβ levels in the cerebellum would have any bearing whatsoever on the treatment of Alzheimer's disease in human patients. Moreover, when the extent and appearance of brain amyloid plaques was examined histologically in these animals, the specification notes that "[m]ajor differences were not seen when the 21F12 and 266 groups were compared with the PBS controls" (p. 78, lines 25-26). The skilled artisan would therefore reasonably conclude that the mAb 266 antibody is not particularly efficacious for the removal of Aβ. Thus, the instant specification is not enabling for a method of treating, delaying the development of, or reducing the risk of Alzheimer's disease using the instantly claimed 266 mAb.

While the level of skill in the art is high, the level of predictability is quite low. Both at the time of filing and presently, the relevant art acknowledges that there is unpredictability in the ability of anti-Aβ antibodies to affect Aβ pathology. For example, Solomon et al. (Progress in Alzheimer's and Parkinson's Diseases, edited by Fisher et al., Plenum Press, New York, 1998, pages 205-211; listed on Applicant's IDS filed 10/16/2006) compare a panel of monoclonal antibodies – 6C6, 10D5, 2H3, 266, and 1C2 – and demonstrate that even with antibodies having similar binding epitopes such as 6C6, 10D5 and 2H3, which all bind to the amino-terminus of Ab, there is variability in the ability of the antibodies to maintain Aβ peptide solubility (see p. 210). Solomon et al. also note that the mAb 266 exhibited only a low protective effect on Aβ peptide solubility, wherein non-soluble Aβ peptide ultimately leads to amyloid-β aggregation and plaque deposition (see p. 210). Additionally, Bard et al. (*Nat Med*, 2000; 6(8):916-919; listed on Applicant's IDS filed 04/26/2004) report that certain monoclonal anti-Aβ

antibodies – notably 16C11 and 21F12 – were completely ineffective both in vivo and ex vivo for reducing Aβ plaque burden in the brains of PDAPP mice (see Figure 1, p. 917 and Table 1, p. 918). Accordingly, the relevant art recognizes unpredictability in the efficacy of anti-Aβ mAbs to elicit therapeutically beneficial effects on pathology caused by amyloid-β.

Therefore, due to the large quantity of experimentation necessary to establish the effectiveness of a humanized version of the 266 antibody for the treatment of Alzheimer's disease or the prophylactic effectiveness of such treatment in susceptible patients, the lack of direction or guidance in the specification regarding the same, the complex nature of the invention, the state of the relevant art indicating unpredictability of the therapeutic effectiveness of particular monoclonal Aβ antibodies, undue experimentation would be required of the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 56, 58, 61-66, 71-73, 77-79, 86, 97, 183, 185-191, 194-196, 200-202 and 205 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,688,651 to Solomon (filed December 16, 1994; listed on Applicant's IDS filed 04/26/2004) as evidenced by Fox et al. (*Brain*, 1998; 121:1631-1639), Fukutani et al. (*J. Neurological Sci.* 1997; 149:177-184) and Plückthun (*Immunol Rev*, 1992; 130:151-188).

Solomon teaches methods of selecting monoclonal antibodies and genetically engineered antibody fragments which prevent aggregation of aggregating proteins, and methods of treating a protein aggregation disease (see paragraph spanning columns 4-5). Such aggregating proteins include amyloid-β, whose abnormal aggregation leads to amyloid diseases such as Down's syndrome and Alzheimer's disease (see column 1, lines 42-51), which are unique to humans, thus meeting a limitation of claims 61 and 186. The antibodies are disclosed to bind to an epitope on the target molecule which is a region responsible for folding or aggregation, and in a preferred embodiment, the target molecule is β-amyloid and the monoclonal antibody is an anti-Aβ monoclonal or genetically engineered fragment thereof (see column 5, lines 30-54). For example, Solomon discloses the use of the anti-Aβ monoclonal antibody (mAb) AMY-33, which was raised against the fragment Aβ1-28 (see column 6, lines 21-26). Solomon teaches that binding of mAb AMY-33 to Aβ prevents self-aggregation of the protein, by

recognition of the sequence 25-28 located in the proposed aggregation fragment comprising the amino acids between 25-28 of Aβ (see column 16, lines 5-8). Accordingly, the mAb AMY-33 would meet the limitation of claims 56 and 183 of an antibody that specifically binds to an epitope within residues 13-28 of Aβ, and because of such binding, AMY-33 would be expected to compete with mAb 266 for binding to Aβ, as recited in instant claims 58 and 185. The disclosed methods directed prevention of protein aggregation would encompass the instantly claimed methods of reducing risk or delaying the onset of Alzheimer's disease (as in claim 183), because preventing Aβ from aggregating in a patient at risk of the disease would certainly lead to both a reduced risk and/or a delayed onset of the disease. Solomon discloses, through the incorporation by reference of Plückthun (see column 16, lines 27-33), engineered antibodies that include single chain antibodies, antibody fragments including Fv and Fab fragments (see pp. 152-158 of Plückthun), bispecific antibodies (see pp. 172-177), and humanized antibodies (see pp. 177), thus meeting recited limitations of instant claims 56, 66, 71-73, 77-79, 183, 191, 194-196 and 200-202. Plückthun also notes that in the production of engineered antibodies, such as single chain or bivalent antibodies, a hydrophobic peptide tail is often added to stabilize the molecule, thus addressing the limitation "wherein a chain of the antibody is fused to a heterologous polypeptide" of claims 86 and 205. Although Solomon is silent with respect to the pharmaceutical compositions comprising the AMY-33 antibody, the skilled artisan would reasonably expect that for therapeutic administration of an antibody molecule, the antibody would have to be contained within a pharmaceutically acceptable solution comprising an

acceptable carrier, such as buffered water or saline, or the like. Accordingly, the teachings of Solomon anticipate the instant invention.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 97, 99 and 164-182 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,589,154 to Anderson (issued December 31, 1996; listed on Applicant's IDS filed 05/02/2006), and EP 613007 A2 by Becker et al. (published August 31, 1994; listed on Applicant's IDS filed 04/26/2004), in view of US 5,593,846 to Schenk et al. (issued January 14, 1997; previously cited).

The claims are drawn to a pharmaceutical composition comprising a human or humanized antibody which specifically binds to an epitope within residues 13-28 of Aβ and a pharmaceutical carrier, wherein the humanized antibody is a humanized version

of the monoclonal antibody 266, and wherein the composition comprises a number of particular components or agents.

Anderson teaches a method for diagnosing the presence of amyloid plaques in an individual which comprises administering to the individual a labeled agent that specifically binds to β-amyloid peptide, wherein the agent is an antibody, or an antibody derivative, that binds β-amyloid peptide (see paragraph spanning columns 4-5). Anderson discloses that where chronic or prolonged administration is desired, the use of non-immunogenic antibodies is preferred, such as humanized antibodies (see column 12, lines 10-25). Anderson also teaches pharmaceutically useful compositions, wherein the antibody or other agent is combined in admixture with a pharmaceutically acceptable carrier vehicle (see column 16, lines 8-11). It would be expected that a pharmaceutically acceptable composition for administration to an individual would comprise a pharmaceutically acceptable diluent, such as water or physiological PBS, as in instant claim 166. Control release preparations (i.e., sustained release) may be achieved, to control the duration of action, through the use of polymers to complex or absorb the agents or polymeric material to incorporate the agents into particles. Such agents include, but are not limited to, macromolecules such as polyesters, polyamino acids, hydrogels, poly(lactic acid) or ethylene copolymers, or colloidal drug delivery systems (see column 16, lines 12-34), thus meeting recited limitations of claims 169 and 170. The skilled artisan would recognize that such agents encompass and therefore render obvious the surfactant agents (i.e., wetting agent, emulsifying agent, etc.) and stabilization agents of instant claims 174-178 and 181. Anderson teaches that antibody

compositions are preferably provided by injection, most preferably by intravenous infusion (see column 16, lines 39-41), thus meeting a limitation of instant claim 171.

Similar to Anderson, Becker teaches the use of anti-Aβ antibodies for both *in vitro* and *in vivo* diagnosis of disease states or biological status in mammals, preferably humans (see column 7, lines 39-44). Becker teaches that the disclosed antibodies include humanized and human antibodies (see column 5, line 51 – column 6, line 21). Becker also discloses pharmaceutical formulations for parenteral administration containing the anti-Aβ antibodies, as well as products for parenteral administration formulated and distributed in solid, preferably freeze-dried form, for reconstitution immediately before use, thus meeting recited limitations of claims 171, 172, 180 and 182. Typical fluids for intravenous administration include physiological saline, Ringer's solution or a 5% dextrose solution, which addresses limitations of instant claims 165-168.

However, neither Anderson nor Becker teach the use of an the monoclonal antibody 266, or of an antibody that specifically binds to an epitope within residues 13-28 of Aβ.

Schenk et al. teach that antibodies specific for the junction region consisting of residues 13-28 of Aβ are useful for the detection of Aβ because they are not cross-reactive with the larger amyloid precursor protein (APP) from which Aβ is derived due to the fact that the site between amino acid residues 16 and 17 is a target for normal proteolytic processing of APP (see column 4, line 63-column 5, line 2, and column 7, lines 31-43). For example, Schenk discloses the monoclonal antibody 266, which was

raised against and recognizes residues 13-28 of Aβ. Schenk also discloses that the methods and compositions of the invention are useful for the diagnosis and monitoring of Aβ-related conditions in patients (see column 4, lines 23-28), such as the *in vivo* detection of Aβ in a patient (see column 10, lines 6-7). Schenk teaches pharmaceutical compositions at column 11, lines 23-40, wherein the pharmaceutically acceptable carrier can be sterile water, alcohol, fats, waxes, and inert solids, as well as adjuvants, buffering agents, dispersing agents, and the like, which would address recited limitations of claims 165-166, 172-173 and 179-182. Schenk similarly teaches that such compositions may be administered parenterally, i.e., subcutaneously, intramuscularly, or intravenously (see column 11, lines 41-45). Again, one of the skill in the art would be well aware of typical diluents for parenteral administration, such as sterile water, physiological buffered saline, Ringer's solution, dextrose solution or Hank's balanced salt solution, as are recited in instant claims 166-168. For example, Schenk notes that a typical composition for intravenous infusion would contain sterile Ringer's solution and the agent (see column 12, lines 5-7).

It would have been obvious to one of skill in the art at the time the invention was filed to combine the teachings of Anderson, Becker and Schenk to arrive at the claimed pharmaceutical composition comprising a humanized or human anti-Aβ antibody that binds to Aβ 13-28. The artisan would be motivated to make such a combination because both Anderson and Becker teach the administration of humanized (or human) antibodies for *in vivo* diagnosis of conditions related to amyloid-β, such as Alzheimer's disease, because there is a long-felt need in the art for a definitive method to diagnosis

Alzheimer's disease pre-mortem. The skilled artisan would also be motivated by the teachings of Schenk, who discloses in vivo diagnosis and monitoring of patients with amyloid-related diseases, such as monitoring for therapeutic effectiveness or disease progression. As the monitoring of patients having, for example, Alzheimer's disease may occur over a period of weeks, months or even years, the skilled artisan would be motivated to used a pharmaceutical composition comprising a humanized or human anti-Aβ antibody because of the lowered immunogenicity of such antibodies, which would decrease the risk of an adverse immunologic reaction with the initial and particularly with subsequent administrations. Further, the artisan would be motivated to use the monoclonal 266 antibody or another antibody binding within the same epitope because Schenk teaches that antibodies binding to this region can differentiate between Aβ and APP, thus giving a more accurate measurement of processed Aβ levels in the body. The artisan would reasonably expect that such a humanized or human 266 antibody (or an antibody with an epitope of Aβ 13-28) would bind to the desired target and provide a level of Aβ in the body for diagnostic purposes because of the demonstrated effectiveness of the 266 antibody to bind to and detect Aβ peptides *in vitro*. Accordingly, the combined references render instant claims 97, 99 and 164-182 obvious at the time the invention was made.

17. Claims 74-76, 81, 85, 92, 197-199, 203-204 and 207 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,688,651 to Solomon (filed December 16, 1994; listed on Applicant's IDS filed 04/26/2004) as evidenced by Fox et al. (*Brain*,

1998; 121:1631-1639), Fukutani et al. (*J. Neurological Sci.* 1997; 149:177-184) and Plückthun (*Immunol Rev*, 1992; 130:151-188), in view of EP 613007 A2 by Becker et al. (published August 31, 1994; on 04/26/2004 IDS) and EP 620276 A1 by Adair et al. (published October 19, 1994).

The teachings of Solomon are discussed above. Briefly, Solomon teaches therapeutic and prophylactic methods of treating Alzheimer's disease using a humanized version of the mAb AMY-33 antibody, which recognizes an epitope within residues 13-28 of Aβ (residues 25-28 in particular), and thus would compete for binding to Aβ with the mAb 266.

However, Solomon does not specifically recite that the administered antibodies or antibody fragments are human or chimeric antibodies, polyclonal antibodies, or particular methods of administration.

Becker et al. also teach methods of treating Alzheimer's disease in humans via administration of anti-Aβ antibodies (see column 7, lines 39-52), wherein the antibodies of the invention include fragments of antibodies, such as Fab, Fab', Fab_2', and Fv fragments, and chimeric, humanized, veneered, resurfaced, or CDR-grafted antibodies (see column 5, lines 51-55), as well as polyclonal or monoclonal human antibodies (see column 6, lines 10-19), which would meet limitations of instant claims 74-76, 81, 197-199 and 203. Becker teaches that genetically engineered antibodies, such as humanized antibodies, are advantageous because they retain the epitope specificity of monoclonal antibodies but are less immunogenic (see column 6, lines 31-40). Becker also teaches that pharmaceutical formulations comprising the anti-Aβ antibodies are

suitable for parenteral administration, such as by intravenous infusion (see column 8, lines 19-42), thus addressing limitations of instant claims 92 and 207.

Adair et al. disclose generic methods of producing humanized monoclonal antibodies from non-human species in order to reduce immunogenicity of the antibodies when they are administered a human (see p. 3, lines 1-10). For example, Adair notes that the use of rodent mAbs as therapeutic agents in humans is limited by the fact that the human subject will mount an immunological response to the mAb and will either remove it entirely or at least reduce its effectiveness (see p. 3, lines 29-45). Adair also teaches that the constant domains of the humanized antibodies may be selected having regard to the proposed function of the antibody when particular effector function may be required. For example, Adair notes that IgG human constant region domains may be used, especially IgG1 and IgG3 isotypes, when the humanized antibody molecules are intended for therapeutic uses and antibody effector functions are required (see p. 6, lines 54-57). Accordingly, the teachings of Adair would address the limitations of claims 85 and 204.

It would have been obvious to one of skill in the art at the time the invention was made to have combined the teachings of Solomon, directed to treatment of Alzheimer's disease using a specific anti-Aβ antibody, with those of Becker et al. and Adair et al. directed to the use of human, humanized, and chimeric antibodies for therapeutic use of monoclonal antibodies, and also to treatment of Alzheimer's disease in the case of Becker. The artisan would be motivated to make such modifications because both Becker and Adair teach that chimeric or "humanized" antibodies are less immunogenic

to humans than the non-human monoclonal antibodies from which they are derived. The artisan would also be motivated to select for an IgG1 constant region isotype for the antibody, as directed to by the specific teachings of Adair noting that such an isotype is particularly useful in therapeutic applications requiring effector functioning of the antibody. The artisan would reasonably expect that such antibodies would be successful for the treatment of Alzheimer's disease because Solomon notes that the AMY-33 antibody was effective to prevent Aβ aggregation *in vitro*. Accordingly, the instant invention is rendered obvious by the combination of the above references.

18. Claims 93-94 and 208-209 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,688,651 to Solomon, in view of EP 613007 A2 by Becker et al. and EP 620276 A1 by Adair et al. as applied to claims 74-76, 81, 85, 92, 197-199, 203-204 and 207 above, and further in view of US 5,731,284 to Williams (filed September 28, 1995).

The teachings of Solomon in view of Becker and Adair are addressed above with respect to claims 74-76, 81, 85, 92, 197-199, 203-204 and 207. However, the references do not teach multiple administrations of the composition or a sustained release composition.

Williams teaches a method of treating injury or degeneration of neurons, such as occurs in Alzheimer's disease, comprising administering a therapeutic agent, in this case the neurotrophic factor GDNF (see column 1, lines 6-11). Williams discloses that the optimal pharmaceutical formulation will be determined by one skilled in the art

depending upon the route of administration and desired dosage (see column 16, lines 57-59). For example, parenteral slow-release formulations are disclosed by Williams (see column 17, lines 3-4), as is repeated daily or less frequent injections of the agent, wherein the frequency of dosing depends on the pharmacokinetic parameters of the agent being administered and the route of administration (see column 17, lines 49-56). The skilled artisan would be aware that Alzheimer's disease is a chronic neurodegenerative disease, and thus artisan would reasonably conclude that it would take multiple doses of the antibody administered over several weeks, months or even years for effective treatment of the disease, particularly so as to maintain an effective level of the humanized antibody in the body.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was filed to administer the humanized AMY-33 antibody for the treatment or prophylaxis of Alzheimer's disease either as multiple dosages over a period of several months or longer or as a sustained release composition, as indicated by the teachings of Williams. In addition to the teachings of Williams indicating multiple administrations or sustained release of a therapeutic agent for the treatment of Alzheimer's disease (AD), the artisan would be motivated to make such modifications to the administration method because the artisan would recognize the chronic nature of AD would require long-term or sustained treatment, as would methods to reduce the risk or delay the development of Alzheimer's disease in prophylactic applications. Further, it would be routine practice to optimize the particular administration parameters to determine the optimal period of treatment (i.e., at least six months), and the skilled

artisan would be motivated to do so based upon "[t]he normal desire of scientists or artisans to improve upon what is already generally known", see MPEP 2144.05. Thus, absent some demonstration of unexpected results from the claimed administration parameters, this optimization would have been obvious at the time of applicant's invention. Accordingly, the combined teachings of the above references render obvious the instant invention.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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May 10, 2007

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